EDITORIAL

When is susceptibility to infections abnormal?

DOI:10.1111/j.1399-3038.2011.01217.x

In this issue of PAI, MacGinnitie et al. (1) address a very important question that sounds simple at first sight but is extremely difficult to answer if one looks closely enough: Which child should be evaluated for possible Primary Immunodeficiency (PID)?

In several countries of the world, 10 warning signs distributed by the Jeffrey Modell foundation are used to select children for an immunodiagnostic workup. However, as the authors state, these warning signs have never been validated scientifically and were based on a CDC consensus meeting of experts in 1994 with the goal to define 10 warning signs for PID. Unfortunately, no prospective studies validating these signs have been performed, and alternative approaches have been discussed.

We have recently published an attempt to define abnormal susceptibility to infections (Table 1).

In addition, we have added two more warning signs, which we felt were important: the red neonate with Graft vs Host Disease or a differential diagnosis (Omenn phenotype, neonatal Hyper IgE syndrome, Comel-Netherton syndrome and others) and disseminated disease with either atypical mycobacteria or BCG (2). Thus, in Germany, many doctors use 12 warning signs. Of course, also these are not at all evidence-based but only based on clinical experiences.

MacGinnitie et al. in their retrospective study analyzed 141 children with at least one of 10 warning signs (WS) present. They identified 32 children as having a PID according to the current international PID classification. Patients with WS present were more likely to have a PID than patients without WS. Only very few children had symptomatic PID (four CVID, two XLA, one SCN, one 22q11.2 deletion). As the authors state by themselves, a number of 7 symptomatic PID patients are by far too small to validate warning signs. A large population of children with known PID could probably better answer the question if WS are present in this population or not. Subbarayan et al. (3) studied 430 children with definite PID and compared them with 133 children in whom detailed investigations failed to establish a PID diagnosis. The strongest identifiers of PID were the family history, the need for i.v. antibiotics for the treatment of bacterial infection/sepsis, and failure to thrive. The message from this study is that WS, either 10 or 12, maybe helpful for early identification of children with PID, but that three of these maybe especially valuable.

Despite these studies, we are still lacking prospective studies performed in children with WS present and in age-matched controls. Unless such data are available, we will have to be satisfied with WS as the currently are.

The overlap of symptoms in atopic children and children with PID indicates the necessity that allergists are trained to identify children with PID and that immunologists are trained to identify children with atopy. Warning signs can be helpful in selecting children for immunological laboratory studies but they should never be used schematically. Many other minor clinical features maybe equally important. Appropriate clinical training should be an essential part of the allergists' specialization. Such a training would give us the chance for more early diagnoses in PID children, which allows us, by appropriate treatment, to prevent irreversible organ damage or premature death. A wonderful goal!

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Table 1. Physiological and pathological susceptibility to infections

Characteristics of infections	Physiological susceptibility to infection	Pathological susceptibility to infection
Incidence	Max. 8 minor infections per year until 3 yr of age, thereafter less frequently	More than 8 minor infections per year until 3 yr of age and beyond
Degree of severity	Slight, minor infections	Severe, major infections*
Course	Acute	Chronic, relapsing
Residues	No	Yes
Relapse with identical pathogen	No	Yes
Opportunistic infection	No	Yes

*Pneumonia, sepsis, meningitis, encephalitis, osteomyelitis, septic arthritis, empyema, deep visceral abscesses (not single unproblematic episodes of cervical lymphadenitis).

References

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